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THE PROCTER & GAMBLE COMPANY
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EXAMINER	
ANDERSON, CATHARINE L	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/078,816
Filing Date: February 19, 2002
Appellant(s): DIEHL ET AL.

Michael P. Hayden
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 13 April 2005.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct. However, box stating the amendment after final as not being entered was incorrectly marked. The amendment to the specification and drawings was initialed as to be entered on 17 February 2005.

The amendment after final rejection filed on 22 February 2005 has been entered.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims 1-20 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

6,515,194	Neading	2-2003
5,947,943	Lee	9-1999
5,922,283	Hsu	7-1999

Chadha V., et al.; "Measurement of Urinary Concentration: a Critical Appraisal of Methodologies" Pediatric Nephrology, vol. 16 (Apr. 2001), pp. 374-382.

Spencer, Daniel; "Subtopic 1: Physical Examination of Urine" Urinalysis website, 20 June 2005.

(10) Grounds of Rejection

The appealed claims are rejected under new grounds of rejection based on the arguments presented in the Appeal Brief stating that the measuring specific gravity is not the same as measuring urine ionic strength.

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4-12, and 14-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neading et al. (6.515.194) in view of Hsu (5,922,283).

With respect to claims 1, 10, and 17, Neading discloses a wearable article, as shown in figure 2, comprising a topsheet 18 and a dehydration indicator 14A, 16. The dehydration indicator 14A, 16 exhibits a visible response elicited by the specific gravity, as disclosed in column 4, lines 1-8. The wearable article is an absorbent article, as shown in figure 2, comprising an outer cover 22, a fluid permeable topsheet 18, and an absorbent structure 20.

Neading remains silent as to the method of measuring specific gravity, and does not explicitly disclose the measuring of the urine ionic strength in order to determine the specific gravity of the urine. Hsu teaches the use of test strips to determine the specific gravity of urine by measuring the urine ionic strength. The test strips comprise an absorbent material impregnated with a reagent that exhibits a color change upon contact with urine to indicate the ionic strength and subsequently the specific gravity of the urine, as disclosed in column 8, lines 3-12. Neading discloses the need for a material that undergoes a color change elicited by specific gravity, as described in column 4, lines 1-4, by contacting the material with absorbed urine, thus providing a motivation to measure any parameter that would allow the determination of specific gravity from a color change. It would therefore be obvious to one of ordinary skill in the art at the time of invention to provide the test strip material of Hsu as the strip of

material disclosed by Neading, to provide an indicator designed for absorption of urine that undergoes a color change elicited by specific gravity.

With respect to claims 2, 3, and 13, the dehydration indicator 14A, 16 provides a qualitative indication of the specific gravity, which can be used to determine dehydration.

With respect to claims 4, 11, 12, and 18, the dehydration indicator 14A, 16 is affixed to, or disposed on, the topsheet 18, as shown in figure 3, and is fully capable of being detached from the topsheet 18.

With respect to claims 5, 6, 19, and 20, the dehydration indicator 14A, 16 comprises an indicium, the indicium being a color change, as disclosed in column 4, lines 1-4.

With respect to claims 7 and 15, the dehydration indicator is disposed on a carrier element, as disclosed in column 3, lines 57-58.

With respect to claims 8 and 14, the dehydration indicator 14A, 16 is covered by a semipermeable membrane 14B, as shown in figure 3.

With respect to claims 9 and 16, the dehydration indicator 14A, 16 is in fluid communication with a fluid transport element 14B, as shown in figure 3.

Claims 3 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neading et al. (6,515,194) in view of Hsu (5,922,283), as applied to claims 1 and 10 above, and further in view of Lee (5,947,943).

Neading, in combination with Hsu, discloses all aspects of the claimed invention but remains silent with respect to the outer cover 22. Neading discloses in column 4, lines 49 and 67, that the indicator comprised in the article is exposed.

Lee discloses an absorbent article having an indicator located therein, as described in column 3, lines 12-15. The outer cover 16 of the article is translucent so the indicator may be easily viewed without removing the article, as disclosed in column 3, lines 46-55. The outer cover 16 provides a barrier to moisture, as disclosed in column 3, line 6, which prevents liquids from leaking from the article and protects the indicator from exterior liquids.

It would therefore be obvious to one of ordinary skill in the art at the time of invention to make the outer cover of Neading as modified by the teaching of Hsu, translucent, as taught by Lee, so the indicator is protected by the cover but still easily viewed without removal of the article.

(11) Response to Argument

In response to the Appellant's argument that Neading fails to disclose measuring ionic strength, and that measuring specific gravity is not the same as measuring urine ionic strength, it is noted that Neading discloses specifically contacting urine absorbed in the absorbent article with a strip of material that then undergoes a color change elicited by specific gravity. While there are methods of directly measuring specific gravity of a liquid, those methods require collecting the liquid in a container, and do not elicit a color change. Use of reagent strips designed to determine the specific gravity of urine is widely known in the art, and such strips comprise material which measures the

urine ionic strength and change color to indicate the specific gravity that correlates to the urine ionic strength. Since the invention of Neading absorbs the urine to be tested, the only viable method for measuring the specific gravity by eliciting a color change in a strip of material is to first measure the urine ionic strength, as taught by Hsu and discussed in the body of the rejection.

In response to the Appellant's argument that Neading fails to disclose a threshold, it is noted that whether or not Neading explicitly discloses the threshold at which the color change or reaction is elicited, the color change inherently occurs at a predetermined threshold. The color change is elicited by a reaction between the chemical indicator or reagent used to show the color change and the urine. The reactivity of the urine will vary with the ionic concentration of the urine, and depending on the reagent, the color change will occur at a specific level of concentration. As with the example given by Neading in column 4, lines 8-12, of litmus paper to measure pH, the reaction that occurs is inherent to the reagent, being an intrinsic property of the reagent, and the color change will occur based on that reaction. Therefore, the predetermined threshold is inherent to the reagent and the color change elicited.

In response to the Appellant's argument that Neading fails to disclose a semipermable membrane, it is noted that the language of the claims is given the broadest reasonable interpretation in view of the specification. While the instant specification discloses examples of materials for use in the instant invention, it does not assign special meaning, such as those cited in the Appeal Brief, to the limitation 'semipermeable membrane.' The fibrous layers of Neading that cover the indicator,

such as the inner layer 18 and fluid transport layer 14, comprise materials that are permeable to liquid but not to large solid particles too big to pass through the material, i.e. semi-permeable. Therefore, Neading discloses a semipermeable membrane, as based on the broadest reasonable interpretation of the claim language.

In response to the Appellant's argument that there is no reason to combine the teachings of Lee with the invention of Neading, it is noted that the translucent outer cover of Lee would provide the additional advantage of protecting the otherwise exposed indicator of Neading, while still allowing the indicator to be visible from the outside.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

C. Lynne Anderson
July 20, 2005

Conferees

Tatyana Zalukaeva

Angela Sykes

Director TC 3700

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Urinalysis

A Professional Development Resource by Daniel Spencer

Subtopic 1: Physical Examination of Urine

All routine urinalysis should begin with a physical examination of the urine sample. This examination includes assessment of **volume**, **odor**, and **appearance** (color and turbidity).

Volume

Urinary volume is dependent upon fluid intake; amount of solutes to be excreted, primarily sodium and urea; loss of body fluids by normal processes, such as perspiration and respiration, and abnormal processes, such as diarrhea; and cardiovascular and renal function. Although the volume of a random specimen is clinically insignificant, the volume of specimen received should be recorded for purposes of documentation and standardization.

Urine volumes can be measured two ways: volumetrically and gravimetrically. That is, the volume is measured with a volumetric cylinder or the volume is estimated by weighing the urine sample in a tared container and assuming that 1g = 1mL of urine.

Odor

Non-pathological, fresh urine has an inoffensive odor. One usually determines the odor of the urine sample by placing ones nose near the orifice of the sample container , moving the air from the container to your nose by gently wafting with your hand, and gently breathing the fumes.

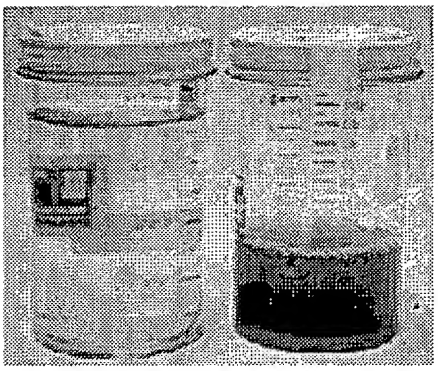
Appearance (color and turbidity)

Color—The color of urine is related, to a large degree, by its degree of concentration. The color of non-pathological urine varies widely from colorless to deep yellow; the more concentrated the urine, the deeper the color. The color of urine is usually described after visual inspection with common color terms. Very often color charts will be available to report the colors in a consistent fashion.

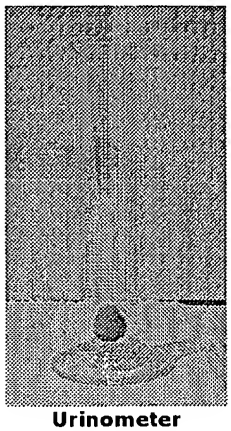
A good clinical history can resolve possible causes of an unusual urine color

Turbidity—Normally freshly voided urine is clear. When urine is allowed to stand, amorphous crystals, usually urates, may precipitate and cause urine to be cloudy. The turbidity of urine should always be recorded and microscopically

explained.

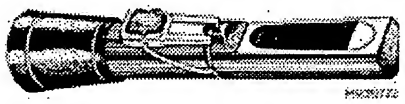


Specific gravity—A hydrometer (**urinometer**) and a suitable container may be used to determine specific gravity.



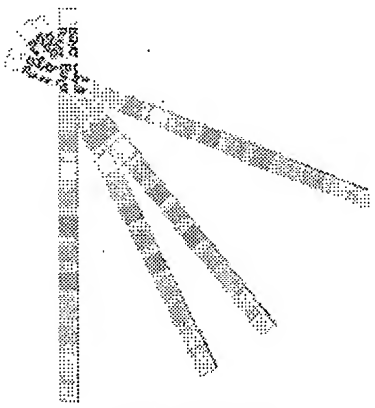
Urinometer

Many laboratories may also be equipped with **refractometers** that can relate density of a solution to specific gravity Refractometers work on the principle that light passing from a transparent medium of one density to a medium of another density, will change its velocity and therefore the direction in which the beam of light is moving. This change in direction, or the bending, o light is called refraction. The refractivity of a solution is dependent, in great part, on the total mass of solids dissolved in that solution. The refractive index scale can be calibrated to measure the specific gravity of most urine sample, that is up to 1.036 g/mL .



Refractometer

An indirect colorimetric method for estimating specific gravity is available on reagent strips ("**urine dipsticks**"). This method uses a pad that contains a complex, pre-treated electrolyte that undergoes a pH change based on the ionic concentration of the urine. This change results in a change of color of the pad. For the Multistix SG-10, specific gravity is measured using an apparent pKachange in the presence of an indicator (dyes) whose colors vary from deep blue-green at low ionic strength to green and yellow-green at higher ionic concentration. This estimate of specific gravity is rapid, simple, and requires no special equipment.



Urine dipsticks

The falling drop method is a direct method of measuring specific gravity that is usually used with automated instruments, such as the Clinitek Auto 2000 (Ames Division, Miles Laboratories, Inc., Elkhart , IN). The CliniTek2000 uses a specially designed column containing silicone oil. Specific gravity is calculated from the time it takes for a drop of urine to fa between two optical gates.

Osmolality—Osmolality is usually measured by an osmometer, most frequently by a freezing point osmometer. Osmolalityis a measure of the number of particles per unit mass, whereas the specific gravity is a reflection of the density (mass per unit volume) of the suspended particles

Clinical Significance—Primary kidney function includes the ability to produce, in the appropriate circumstances, either a concentrated urine (osmolality>850 mOsm/kg) or a dilute urine (osmolality<100 mOsm/kg). A random urine whose osmolality>600 mOsm/kg is presumptive evidence of an ability to concentrate urine. The urine osmolality thus is part of the mechanism of maintaining water balance. In the presence of excess free water, the kidneys will produce a dilute urine, while in periods of water lack a concentrated urine is produced.

Loss of concentrating ability is often one of the earliest signs of kidney disease, clinically evidenced as nocturia (needing to void at night) and polyuria (increased volume of [usually dilute] urine).

Pediatr Nephrol (2001) 16:374–382

INVITED REVIEW

Vimal Chadha · Uttam Garg · Uri S. Alon

Measurement of urinary concentration: a critical appraisal of methodologies

Received: 14 August 2000 / Revised: 24 November 2000 / Accepted: 27 November 2000

Abstract The measurement of urine concentration provides information concerning the kidney's ability to appropriately respond to variations in fluid homeostasis. It also assists in the interpretation of other tests performed on the same urine specimen. The gold standard of estimating urinary concentration is the measurement of its osmolality; however, this procedure is not readily available to the practicing physician. Therefore, urine concentration is usually determined by measurement of its specific gravity (SG), which provides a fair estimate of urine osmolality. Over the years numerous tests have been developed to measure urine SG in a simple, quick, reliable and easily available method. These tests measure SG either directly (e.g., gravimetry) or by indirect methods (e.g., refractometry and reagent strip). All these tests have certain limitations based on their underlying physical principles. Specific gravity as measured by refractometry is influenced by proteinuria, such that for each 10 g/l protein the SG increases by 0.003. SG is also influenced by glucosuria such that it increases by approximately 0.002 per 10 g/l glucose when compared with urinary osmolality. Unlike osmolality, which is only affected by the number of particles, refractometry is affected by number, mass and chemical structure of the dissolved particles; hence large molecules like radiographic contrast or mannitol will increase SG relative to osmolality. The reagent strip is minimally affected by glucose, mannitol or radiographic contrast. However, it is affected by urinary pH such that only urine in the pH range of 7.0–7.5 can be correctly interpreted. The measurement of SG by reagent strip is based on the ionic strength of the urine and thus is significantly affected by the ionic composition of the urine and by proteins which have an electric charge in solution. In our experience, SG measured by the refractometer is consistently more accurate than the reagent strip. For the clinician who is interpreting urine SG results, it is important to be aware of these limitations and understand the reasons for possible potential errors of each particular method.

Keywords Urine · Osmolality · Specific gravity · Refractometry · Urinometer · Reagent strips

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Introduction

Even long before the practice of modern medicine, urine has always been examined for clues to the illnesses. The physical examination of any patient (more so the one with kidney disease) is considered incomplete without urinalysis. The measurement of urine concentration is an integral part of urinalysis and provides important information on the kidney's ability to respond to variations in fluid homeostasis, which under normal physiologic conditions are determined mainly by fluid intake. Furthermore, knowing how dilute or concentrated a urine sample is helps in the interpretation of the results of the other tests performed on the same specimen [1]. For instance, a mild degree of proteinuria might be of significance in dilute urine, in contrast to a concentrated sample. Similarly, screening for drugs/toxic chemicals in a dilute urine sample may give false negative results. Additionally, provided that there is no intrinsic renal disease, abnormal adrenal or posterior pituitary function, urine concentration is considered a useful guide to the hydration status [2]. The "gold standard" of urine concentration determination is the measurement of its osmolality. However, in practicality urine concentration is commonly estimated by measurement of its specific gravity (SG) either by a direct method (gravimetry) or by an indirect method (refractometry, reagent strip).

The present review is an appraisal of the current methods used for assessing urine concentration. Emphasis has been laid on understanding the basic physical principles and the limitations of the various tests. Reasons for possible potential errors are highlighted.

Osmolality

Osmolality is the measure of total solute concentration which is dependent only on the number of particles in the solution under study. It is affected neither by the size (weight) nor by the charge of the particles. Osmolality (concentration per kilogram of solution) differs from osmolarity (concentration per liter of solution) in that the latter is affected by changes in the solution's temperature whereas the former is not. While the concentration of most substances in the urine is expressed in solute per volume of solvent (i.e., mmol/l), the osmotic activity of the urine is conventionally measured in milliosmoles per kilogram (1000 mosmol=1 osmol). However, this variability is of no clinical significance as the difference between osmolality and osmolarity is negligible for aqueous solutions of low concentrations like body fluids [3].

The fact that one mole of any substance contains the same number of molecules (6.03×10^{23}) implies that when 180 g glucose, 60 g urea or 113 g creatinine is dissolved in 1 kg pure water they have equal osmolality (=1 osmol). In case the parent molecule dissociates in the solution, the osmolality is multiplied depending on the number of dissociated particles (e.g., 1 mole of sodium chloride (NaCl) is equal to 2 osmol as it dissociates into Na^+ and Cl^-). Thus if two substances are present in the same concentrations by weight (g/kg water), the substance with a lower molecular weight will have a greater osmotic activity, and if it dissociates on dissolution the osmotic activity will increase accordingly (e.g., the osmotic activities of 180 g glucose, urea or NaCl in a kilogram of water are 1, 3 and 6.7 osmol, respectively). For this reason, larger and heavier molecules like protein and radiocontrast agents have a minimal effect on osmolality.

Clinically, osmolality is most commonly measured by freezing point or vapor pressure depression. The specimen needs to be centrifuged to remove any particulate matter and a drop of the specimen is then loaded in the instrument, which measures its freezing point and converts it directly to the osmolality reading by the following relationship: 1 osmolal solution in water freezes at a temperature 1.86°C lower than that of pure water.

Specific gravity

The SG of the urine is the ratio of the density of urine to that of pure water at a constant temperature. In addition to the number of particles, the SG is also affected by the molecular mass (molar mass) of the particles. Therefore, the presence of heavy molecules like radiocontrast agents and abnormal concentrations of glucose and protein in the urine cause a disproportionate increase in SG as compared to its osmolality. The SG can be measured either directly (gravimetry) or by indirect methods like the change in the refractive index (refractometry) or by change in pH of a polyelectrolyte (reagent strip).

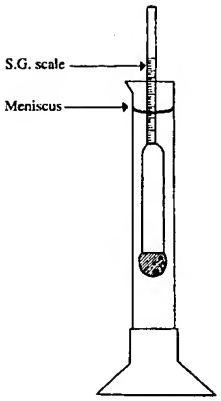

Fig. 1 The urinometer. The SG is read at the bottom of the meniscus

Gravimetry

The measurement of the urine SG based on gravimetry had in fact begun as early as the seventeenth century by comparing the weights of equal volumes of pure water and urine [4]. Even today, weighing aliquots of known volumes of urine on an analytical balance provides the most precise measurement of specific gravity [5]. However, this method is not practical for routine use. Even though a number of gravimetric methods have been evaluated (e.g., falling drop, gravity beads), most clinicians are familiar only with the urinometer.

Urinometers (Fig. 1) are basically hydrometers designed to measure the density of urine by the buoyancy of a plummet with a calibrated stem, which usually is in the form of a folded piece of paper placed inside the stem which can become displaced with rough usage. The calibration is done empirically to measure the SG of urine at a specific temperature (usually 16°C) [6, 7]. As urinometers are made of glass they need to be handled carefully to avoid breakage and injury. They also require periodic standardization with pure water and standard solutions of known relative densities to avoid errors. The glassware used during SG measurement should be clean and free from detergents, and the urinometer should float freely in the measuring cylinder. In cases where the urine sample is insufficient for the urinometer to float freely, the urine should be diluted with distilled water and the result corrected for the dilution factor (e.g., if diluted with an equal volume of distilled water the last two digits of the urinometer reading are doubled). The reading is taken at the eye level at the bottom of the meniscus with the urinometer in a vertical position. Additionally, the urinometer should be cleaned and dried between uses to prevent samples from carrying over. The SG measured by the urinometer requires correction for temperature and presence of abnormal urinary constituents like pro-

tein and glucose [6, 7], as discussed later. Despite all these limitations, urinometers were in fact the first really convenient method available to clinicians for measuring urine SG. However, they are now mostly outdated due to reasons of maintenance, safety and convenience.

Refractometry

Refractometry is an indirect estimation of SG by measurement of the urine's refractive index. The refractive index is the ratio of the velocity of the light in air to the velocity of light in solution (in this case urine). This change in velocity causes deviation (refraction) in the path of light. The degree of refraction is proportional to the number and type of particles (the chemical structure of the molecule and number of double bonds) dissolved in the urine.

The refractometers are also known as the total solid (TS) meters and they work on the principle of critical angle [8]. The critical angle is the maximum possible incident angle at which a ray can enter a second medium, and become refracted. All rays with an incident angle less than the critical angle are refracted, whereas rays with an angle greater than the critical angle are not. When a screen is placed in front of the emerging (refracted) rays it shows an illuminated and a dark field with a sharp and distinct demarcation between the two. The demarcation line is formed by the refracted critical ray and moves with the change in refraction of the critical ray. A scale is placed on this screen which is calibrated directly to read the SG. The simplified optical path of the TS meter and the diagrammatic representation of the screen visible through the eyepiece are shown in Fig. 2. The SG scale has been established by known specific gravities of urine determined by other methods.

As shown in Fig. 2 a thin film of urine sample is placed between the frosted coverplate and the reference glass. The SG is read directly from the scale visible through the eyepiece. Although refractometers offer the advantage of SG determination on a very small volume of urine, in general they are heir to the same errors of interpretation as is the urinometer, and the deviations are in the same direction and of similar magnitude (as discussed later). Like urinometers, they also need to be cleaned and dried in between uses to avoid the carryover of specimens.

Reagent strips

The solid phase indicator for SG determination was introduced in the early 1980s by Ames, Division of Miles Laboratories, and was later incorporated into the multiple assay format of the N-Multistix Reagent Strips. The method offers convenience, disposability and ability to determine the SG simultaneously with other tests on a small urine sample. The reagent strip is dipped in a freshly voided urine sample and reading for SG is done

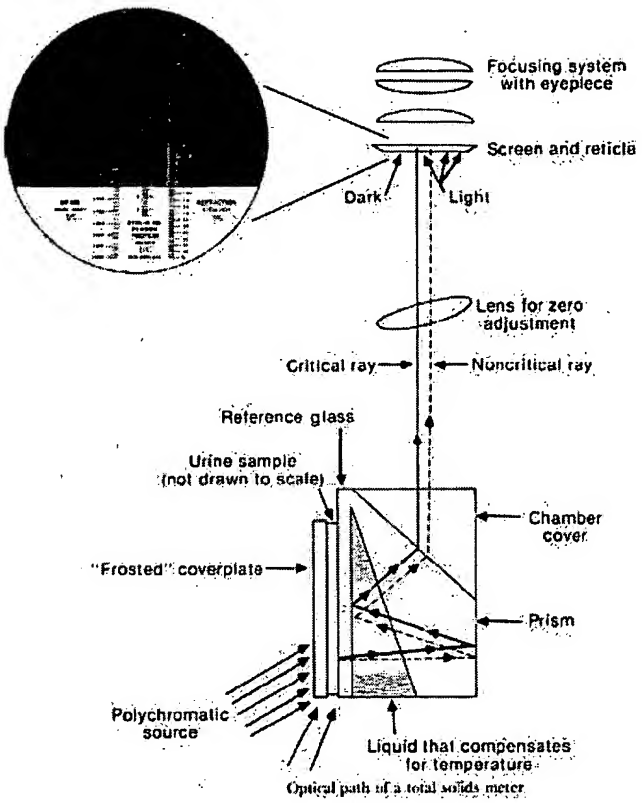

Fig. 2 Schematic diagram showing the optical path of a total solids meter and the screen with the specific gravity scale (reprinted with permission from ref. [8])

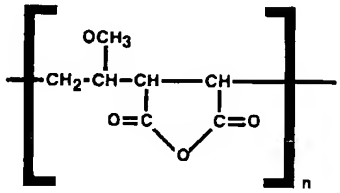

Fig. 3 Chemical structure of the monomer unit of the strip reagent

between 45 and 60 s. Currently the strip can be read either visually by comparing the color change on the reagent area with the color chart on the bottle label, or by a strip reader (Clini-Tek, Bayer Co., Elkhart, IN). The strip reader eliminates incorrect time-to-read errors, avoids the variability of results obtained by visual observation and can be connected to a computerized data collecting system. Additionally, it automatically corrects the SG for urine pH as discussed later.

The key ingredient of the reagent strip is a polymer of methyl vinyl ether/maleic anhydride. The chemical structure of the monomer unit is shown in Fig. 3. The polymer chain consists of carboxylic acid residues (Fig. 4a). During manufacturing the polymer is partially titrated with sodium hydroxide leading to dissociation of some of the acid groups. As these dissociated groups

bear a negative charge and repulse each other, they tend to be most distant from each other (Fig. 4b). The neighboring acid groups can still be forced to dissociate by addition of more alkali, signifying that the neighboring acid groups are weaker acids (higher pK_a values) than those which are situated farther from the originally dissociated groups. The acid groups in the polymer thus have a range of pK_a values.

When this partially dissociated polymer is placed in a salt-containing solution like urine, the cations in the solution are attracted to the negative ionized acid groups on the strip and form a protective cloud around the dissociated acid groups and shield them from their neighbors (Fig. 4c). As a result, neighboring acid groups are now free to dissociate. The dissociation of these new acid groups releases protons in proportion to the ionic concentration of the urine specimen [9]. The released protons react with a pH indicator (bromothymol blue) present in the strip, resulting in a color change. The pH indicator in the fresh unused strip is in basic form (blue color) and changes its color through different shades of green and finally to yellow when the local pH is reduced. The color change is compared to that on the chart, which is labeled in specific gravity values from 1.000 to 1.030 in increments of 0.005. The test thus indirectly measures the SG from the ionic strength of the urine sample and works on the presumption that the ionic and non-ionic constituents of the urine are present in a constant proportion.

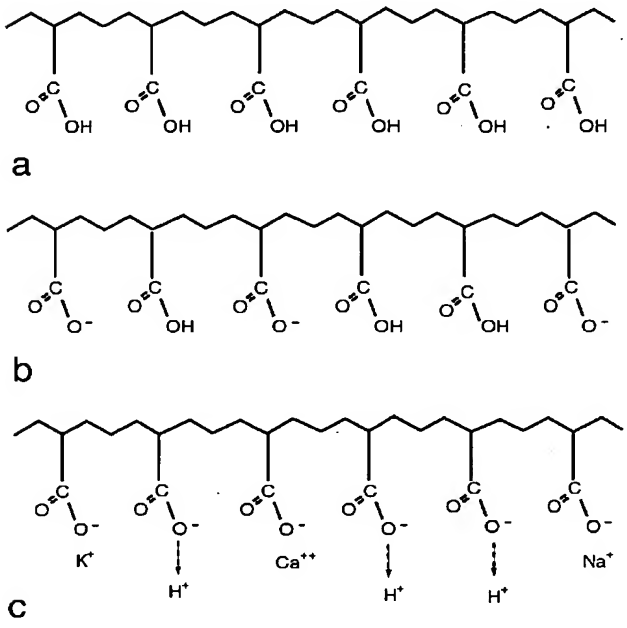

Fig. 4 Schematic representation of changes in the polyacid of the strip reagent. **a** Undissociated polyacid; **b** partial ionization of acid groups after treatment with NaOH; **c** formation of counterion cloud around dissociated acid groups resulting in ionization of adjoining groups with release of H^+

Discussion

The urine is a complex mixture of organic and inorganic compounds, which can be either ionic or non-anionic, in greatly varying proportions. The approximate daily urine solute composition in an adult is shown in Table 1 [10]. In a normal urine the sum of osmoles contributed by urea, sodium, potassium, ammonia, chloride and other anions, or for the purpose of convenience urea + 2× ($Na+K+NH_4$), accounts for almost all of the osmotic activity (Table 1). The determination of urine osmolality is the most specific measure of urine concentration as it is the closest to the physiology of urinary concentration. This is because the kidneys concentrate the urine based on the osmolal gradient and they can by no means differentiate between the different molecules responsible for that gradient. The measurement of urine osmolality, however, requires laboratory support and is not readily accessible to the practicing physician. As a result clinicians usually rely on urine SG for estimating its concentration.

The specific gravity in general is considered a valid estimate of urine concentration and can be converted to approximate osmolality by the following equation:

$$\text{mOsm/kg } H_2O=(SG-1.000)\times 40{,}000 \quad (1)$$

Thus, SG readings of 1.001 and 1.030 are equivalent to osmolalities of 40 and 1200 mosmol, respectively. This relationship, however, is distorted in the presence of abnormal urinary constituents like glucose or protein. Moreover, it is important to note that even variations in

Table 1 Composition of normal adult urine

Component	Total amount in 24 h	Total milliosmoles in 24 h (mean)	Average % contribution to urine osmolality
Sodium	100–200 mEq	100–200 (150)	19
Potassium	50–70 mEq	50–70 (60)	7
Ammonia	30–75 mEq	30–75 (52.5)	6
Other cations	10.5–23.5 mEq	10.5–23.5 (17)	2
Chloride	100–250 mEq	100–250 (175)	21
Other anions	60–220 mEq	60–220 (140)	17
Urea	6–18 g	100–300 (200)	25
Creatinine	0.9–1.8 g	8–16 (12)	1.5
Uric acid	250–750 mg	1.5–4.5 (3)	0.3
Amino acids	80–150 mg (nitrogen)	6–11 (8.5)	1

Note that 90% of the total mean osmolality (818) is due to urea + 2 × (sodium + potassium + ammonia)

normal urinary composition can influence the SG determination as discussed below.

Influence of normal urinary constituents on SG measurement

Variations in the amount of predominant solutes present in normal urine can influence the urinometer SG readings; for example, phosphates, sulfates and bicarbonates produce rather dense solutions, which, for a given osmolality, raise the specific gravity considerably more than chloride salts, ammonium salts, or urea [11]. Similarly, as the refractive indices of various solutes differ from each other, they can influence the refractometer readings. Indeed a preliminary study reported that in equiosmolar urines the refractometer SG readings are lower when salt is the predominant solute and higher when urea is the predominant solute [12].

The influences of variations in normal urinary composition are apparently much more marked on the reagent strip method. As this method is based on the ionic strength of urine, variations in ionic composition have a significant impact on the SG reading [13]. The basic underlying principle of this method presumes that the ionic and non-ionic constituents in urine are present in constant proportion. However, in practice this is not always true. For instance, the urine from young children has a lower concentration of urea [14] and a higher proportion of ionic constituents [13]. As the SG reading by this method is directly proportional to the ionic concentration of urine [9, 15], the SG reading is higher when ionic constituents form the major proportion of osmolality and vice versa. Furthermore, for the same total ionic concentration, different ions influence the SG reading by variable magnitude. These effects were well demonstrated in an experimental study [13]. In urine specimens with constant osmolality, cations like NH_4^{2+}, Ca^{2+} and Mg^{2+} increased the SG reading disproportionately in comparison to Na^+ and K^+. Among the anions, a similar enhancing effect was seen with phosphates and citrate in comparison to chloride, while acetate, lactate, urate, oxalate and sulfate caused no deviation. In the same study ketone bodies were reported to decrease the reagent strip SG reading [13].

Influence of abnormal urinary constituents on SG measurement

The presence of protein or glucose in the urine causes a disproportionate increase in SG as measured by either the urinometer or refractometer, and requires correction. For both methods the recommended correction factors are subtraction of 0.003 and 0.004 SG units for each 10 g/l protein and glucose, respectively [7, 16]. The correction factor for protein is logical as 10 g/l protein increases urine SG by 0.003 while its impact on osmolality is negligible (only 3 mosmol) [1, 4]. However, the same is not true for glucose, as 10 g/l glucose while increasing the SG by 0.004 also increases the osmolality by approximately 55 mosmol (180 g/l glucose = 1000 mosmol, vide supra). Therefore, application of the recommended correction factor of 0.004/10 g/l glucose ignores the contribution glucose makes to the osmolality. For example, in a patient whose urine glucose concentration is 56.3 g/l, the urine osmolality measured 814 mosmol/kg; 38% of this is contributed by glucose (56.3 g/l glucose = 313 mosmol). The refractometer SG reading on this sample is 1.034, and after correction by the recommended factor (0.004/10 g/l) it is 1.012. The SG value of 1.012 corresponded to an estimated osmolality of 480 (vide supra), which is approximately the osmolality had this urine been completely free of glucose (814–313=501). The true measured osmolality (814) was thus underestimated by over 300 mosmol. Note that the presence of 56.3 g/l glucose increased the osmolality from 501 to 814 (an increase of 62%) and the SG from 1.012 to 1.034 (an increase of 180%), thus demonstrating the disproportionate increase in the SG as compared to osmolality. Furthermore the degree of this discrepancy is influenced not only by the amount of glucose but also by urine concentration. For instance, the presence of the same quantity of glucose in a dilute urine results in a greater percentage change in both osmolality and SG compared with concentrated urine. Based on the above example and similar results in other patients (data not presented), we recommend a correction factor of 0.002/10 g/l glucose. This correction factor is more appropriate than the factor of 0.004 as it corrects the SG reading to a closer value to the measured osmolality. In the case of the above example, a correction factor of 0.002 gives a corrected SG value of 1.023 (= osmolality of 920), which is closer to the measured osmolality of 814. Further studies to substantiate the revised correction factor are needed.

The reagent strip SG is reportedly not affected by glucose. In an experimental study, addition of 1 mol (180 g) of glucose to 1 l urine caused a small increase in the reagent strip SG. This increase was 11% of that observed with the urinometer [17]. In contrast, presence of proteins has a marked influence on the reagent strip SG. Proteins in concentration of 1 g/l, which have a negligible influence on urinometer/refractometer SG, increase the reagent strip SG by 0.005, which is more than 15 times of that seen with the former methods (0.0003 per 1 g/l). The proteins increase the reagent strip reading by virtue of their being ampholytes (i.e., bearing an electric charge when in solution). Therefore, one study suggested a correction factor of 0.005 per 1 g/l protein for the reagent strip reading [15]. However, in a group of patients with proteinuria, we did not observe any consistent relationship between the degree of proteinuria and the change in SG readings (Table 2). In contrast, the refractometer SG in all of the ten patients (correction was required in three patients) was within ±0.005 units of the estimated SG value. The relationship between urine protein concentration and its interference with the reagent strip SG might not be as simple, as the electric charge on a protein molecule varies with a change in pH [18]. The

Table 2 Relationship between urine osmolality and SG in patients with proteinuria

No.	Patient	Proteinuria (g/l)	pH	Osmolality	Estimated SG[a]	Refractometer SG (postcorrection)[b]	Reagent strip SG
1	JB	0.25	6.0	215	1.005	1.005	<1.005
2	BA	0.27	5.0	486	1.012	1.013	>1.030
3	SP	0.55	6.5	1028	1.026	1.027	1.020
4	IC	0.67	5.0	422	1.010	1.010	1.015
5	LR	0.80	8.5	231	1.006	1.007	1.010
6	TW	1.05	8.0	340	1.008	1.007	1.015
7	WA	1.42	8.0	492	1.012	1.012	1.020
8	JC	3.83	5.0	406	1.010	1.011 (1.010)	1.020
9	BJ	6.39	5.0	499	1.012	1.015 (1.013)	>1.030
10	AA	6.48	6.5	279	1.007	1.011 (1.009)	1.015

[a] Estimated SG: based on osmolality (osmolality/40,000+1.000) [1]
[b] Correction factor: –0.003 per 10 g/l protein; applied in patients 8–10

influence of proteins on the reagent strip method is, therefore, both concentration and pH dependent.

Apart from glucose and protein, which are the two commonly seen abnormal urinary constituents, both the urinometer and refractometer methods are significantly affected by other heavy molecules such as radiographic contrast materials, mannitol and dextran [7, 19]. The reagent strip is not influenced by them [20].

Influence of temperature

The density as well as the refractive index of a solution is influenced by changes in temperature. The SG measurement by both the urinometer and refractometer is, therefore, sensitive to changes in temperature. In contrast, temperature has no influence on the reagent strip. Urinometers are calibrated at a specific temperature (usually 16°C) and a correction is recommended if the urine is warmer or colder than this temperature [21]. The urine SG may be significantly underestimated if it is measured at or near body temperature (a reading of 1.018 at 37°C represents a true value of 1.025 at 16°C). Two methods of correcting the SG have been advocated and passed from one textbook to the next. The first allows the urine to cool to room temperature before the reading is taken. This method, however, is imprecise as room temperature varies from place to place and the method is especially impractical and meaningless in the tropics where the ambient temperature is high. Furthermore, leaving the urine sample exposed can also lead to evaporative losses thereby increasing the density of the urine. The second method uses a correction factor of 0.001 for every 3°C difference from the specified temperature (addition for warmer and subtraction for colder samples) [21]. However, in an experimental study the relationship between SG and temperature was found to be quadratic rather than linear and demonstrated that the SG was significantly affected only by temperatures greater than 15°C [22]. The recommended correction for urinometer SG is, therefore, not justified at lower temperatures. However, when a precise determination of SG is required while using the urinometer one may need to simultaneously measure the urine temperature. No correction is required for refractometers as they are already temperature compensated [8].

Influence of pH

The basic principle of the reagent strip method is dependent on local pH changes over the strip. Not surprisingly, the results of the reagent strip readings are strongly influenced by urine pH (falsely low results are read in urines with high pH and vice versa) [13, 23]. The manufacturer recommends an adjustment factor of +0.005 for a urine pH equal to or higher than 6.5. When read by the strip reader the SG reading is automatically corrected by the addition of 0.005 to urine specimens with a pH≥6.5. No correction factor is recommended for acidic urine pH; however, 0.005 was subtracted for acidic pH≤6.0 in one of the studies [23]. Whereas in one study the addition of 0.005 value to urines with pH≥6.5 improved the correlation between reagent strip readings and those obtained by refractometer and urinometer [24], other studies failed to demonstrate similar results [13, 23]. Dorner [13] showed that while the SG values for urines with pH≥8.0 are only partially corrected, those with a pH of 6.5 get overcorrected. The SG values in strongly acidic urines (pH<5.0) are always observed to be too high. Thus the only urine specimens which were appropriately corrected were those with pH range of 7.0 to 7.5. Based on the above, urines with pH at both ends of the spectrum are considered unsuitable for SG determination by the reagent strip.

Influence of patient age

Urine samples provided by young children and infants are often not enough to measure their SG by the urinometer. Before the introduction of the reagent strips their SG has usually been measured by refractometers. While evaluating the correlation between the refractometer measured SG and the osmolality it was observed that at the same osmolality younger children had higher SG readings as compared to older children and adults (Fig. 5) [14, 25]. A similar observation of a higher SG reading at the same osmolality was also made with the reagent strip method [13]. The reason for this discrepancy is likely because of the differences in urine composition in young children, which has significantly higher concentrations of free amino acids [26], low molecular weight proteins like microglobulin [27] and lower levels of urea [14],

leading to changes in refractive indices, and reaction with the reagent strip. The low concentration of urea with associated reciprocal increase in the ionic constituents of young children's urine results in higher reagent strip readings (vide supra). Although the same changes are expected to cause lower refractometer SG readings, in reality refractometer SG readings in young children are higher due to high concentrations of free amino acids and low molecular weight proteins in their urine. This discrepant association between SG and osmolality shows a rapid progression towards the adult pattern during the first 2 years of life and is completed around 5 years of age [25]. It is, therefore, obvious that the equation used for estimating osmolality from the SG value in older children and adults is not valid for younger children. This could be one of the possible explanations for the poor correlation observed in newborns between osmolality and refractometer SG [28] or reagent strip [29, 30]. On the other hand, Hensey and Cooke showed a good correlation between reagent strip and refractometer measured SG in 100 newborns [31]; however, one has to remember that any comparison should ideally be done with urine osmolality, which is the "gold standard."

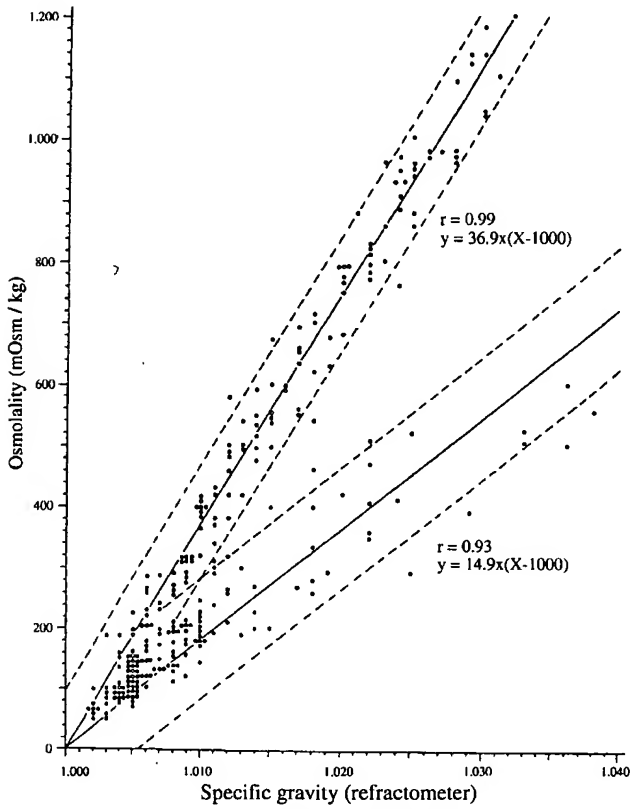

Fig. 5 Relationship between refractometer SG reading and osmolality of urine in newborn infants (•, r=0.93) and in older children (o, r=0.99). *Dotted lines* indicate 95% prediction limits for individual observation (reprinted with permission from ref. [14])

Influence of diet and certain disease states

Unusual dietary patterns either by choice or because of medical conditions such as strict vegetarianism or salt and/or protein restriction as well as exclusive milk as in young children can alter the composition of urine. In subjects on low salt diet, less than normal amounts of sodium and chloride in the urine result in a preponderance of phosphate salts [19]. Though these changes in the urine composition can influence all the methodologies of measuring SG, they have been reported to give false results with the reagent strip method [16, 32]. Similarly certain disease states like hyperparathyroidism, salt losing nephropathy and hypercalciuria can have abnormal ionic urine composition resulting in incorrect SG results, especially with the reagent strip method as this method is directly dependent upon the ionic composition of the urine.

Summary

Based on the above discussion it is clear that numerous factors can influence the SG measurement in a manner unique to the particular method used. The relationship between SG and osmolality, therefore, is at best only a

Table 3 Comparison of different methods of SG determination

Characteristics	Urinometer	Refractometer	Reagent strip
Principle	Gravimetry	Refractive index	Ionic composition
Accuracy and precision	Low	High	Low
Reproducibility	Low	High	High
Convenience	No	Yes	Yes
Calibration requirement	Yes	Yes	No[a]
Possibility of sample carryover	Yes	Yes	No
Interference by:			
Temperature	Yes[b]	Yes[c]	No
Glucose	Yes[b]	Yes[b]	Minimal
Protein	Yes[b]	Yes[b]	Yes[d]
Miscellaneous[e]	Yes	Yes	No
pH	No	No	Yes
Ionic composition	Minimal	Minimal	Significant
Patient age	No available data	Yes	Yes

[a] Calibration only for strip reader
[b] For correction factor see text
[c] Temperature compensated
[d] Variable and pH dependent
[e] Radiographic contrast material, mannitol, dextran, etc.

good approximate. However, in the absence of an easy access to osmolality measurement, most practicing physicians have to rely on the measurement of SG. The choice of a particular method for measuring urinary concentration is usually based on factors which affect the reliability of the results (accuracy, precision, freedom from interferences) and those which affect the efficiency of the method (time required for the measurement, ease of the measurement, cost of equipment involved). Valid data are essential in making medical decisions; accuracy and precision of the particular test are, therefore, of the utmost importance. Furthermore misleading or inaccurate information can result in an unnecessary financial cost to the patient, the insurance carrier or the laboratory. A comparison of the characteristics of the three commonly used methods utilized to measure urine SG is shown in Table 3.

The urinometers are currently of only historical importance. They are cumbersome to use, require a large volume of urine and their accuracy and precision were found to be questionable [7, 21]. The urinometers were largely replaced by refractometers, which are easy to use, are temperature compensated, and require a small volume of urine. The refractometer SG readings, in comparison to reagent strip, have been shown to have a better correlation with osmolality results [16, 33, 34]. Also, there was no difference in the time required to measure SG by either the refractometer or the reagent strip [23]. However, the usefulness of the refractometer SG in predicting urine osmolality during the neonatal age group was found to be questionable [28].

The reagent strip method was introduced in the early 1980s and has been popularized based on its convenience of usage, disposability, and lack of interference by temperature, glucose and other heavy molecules such as radiographic contrast material and mannitol. It is also reported to have a good correlation from lot to lot and minimum reader to reader variability [24]. However, the current studies are divided regarding their accuracy and clinical value. The literature is equally divided between favorable [9, 13, 15, 24, 31, 35–43] and unfavorable studies [17, 23, 29, 30, 33, 44–46]. Unfortunately many of these studies made their conclusions based on a comparison of the reagent strip with either urinometer and/or refractometer SG readings instead of comparing it with the "gold standard" of osmolality [9, 17, 23, 24, 31, 35, 37–39, 45, 46]. Moreover, even the studies which compared the reagent strip results with osmolality [15, 29, 30, 33, 36, 40–42, 44] were equally divided in their conclusion, only five of them [15, 36, 40–42] showing favorable results. One of these [42] was a report by Miles Laboratories Ltd. (the manufacturer of the reagent strip).

The other significant flaw with most of the studies evaluating the reliability of the reagent strips is having based their conclusion on regression analysis [9, 15, 17, 29–31, 33, 36, 43, 44, 46]. It is important to note that close correlation by regression analysis is not an accurate way of comparing two methods of clinical measurement [47]. For example, in the study by Assadi and Fornell [30], the osmolality value ranged from 130 to 600 for a single SG value of 1.010, while the value of "*r*" was 0.88. In another study (reagent strip vs refractometer), 28% of the values differed from each other by more than ±0.005 despite an "*r*" value of 0.80 [23]. The more valid method for such clinical measurement comparisons is percent error analysis. Only a limited number of studies analyzed their data based on percent error analysis [23, 24, 35, 37, 38, 45]. Furthermore, the range of deviations in the reagent strip SG values caused by urine pH and its ionic composition places a serious limitation on its reliability.

Instead of utilizing a chemical reaction, one of the latest automated urine chemistry reagent strip analyzers has incorporated a fibro-optic refractive index technology for SG measurement [48]. This method is claimed to be more accurate than the solid phase polyelectrolyte method of the reagent strip. However, this machine is suitable only for the high-volume urinalysis laboratory and further studies are needed to substantiate its superiority.

In our experience (unpublished data), SG measured by refractometery is consistently more accurate, and the deviations caused by the presence of glucose and protein in the urine occur in a predictable manner. On the other hand, on many occasions the reagent strip results behave in an unpredictable manner even in urine specimens completely free from known interfering substances. The reasons for such anomalies are still far from clear.

In conclusion, measurement of urinary osmolality should be the preferred method whenever an important clinical decision depends on the accurate determination of urine concentration. Measurement of osmolality should also remain the method of choice during the neonatal period. In most other situations, measurement of SG by refractometery provides the most accurate estimation of osmolality relative to other methods. Nevertheless, due to its convenience it seems that in spite of its deficiencies the automated reagent strip method will become more and more popular. Whichever method for determining SG is used, knowledge of its underlying principle and shortcomings (Table 3) can help the clinician in judicious interpretation of the results.

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